Rho activation and subsequent shape change-induced lineage commitment? Or, does an external mechanical force initiate the activation of Rho in stem cells? How does cell shape change promote Rho activation? The identification of additional Rho pathway components in this context should help to address these questions, and the identification of small molecular compounds that can influence components of this pathway could eventually yield drugs that are effective in human diseases that involve tissue remodeling as well as in the engineering of tissues in vitro from isolated stem cells.

Jeffrey Settleman
Massachusetts General Hospital Cancer Center and
Harvard Medical School
149 13th Street
Charlestown, Massachusetts 02129

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HIV-1 Vpu: Putting a Channel to the TASK

Vpu is an HIV-encoded protein that enhances virus release. Previously, this activity was correlated with an intrinsic ion channel activity of Vpu. In this issue of *Molecular Cell*, Hsu et al. (2004) propose an alternative mechanism: they suggest that Vpu functions by inhibiting another ion channel, TASK-1.

Lentiviruses are unique among retroviruses in that they encode a series of proteins not commonly found in other retroviruses. These include the transcriptional activator Tat, the RNA transport modulator Rev, as well as Nef, Vpr, Vif, and Vpu which are generally referred to as accessory proteins. Over the past one-and-a-half decades lentiviral accessory proteins have been the subject of intense research, and much progress has been made in understanding their role in virus replication and pathogenesis. It turns out that all of the HIV accessory proteins are multifunctional. The versatility of these proteins is achieved by a surprisingly simple mechanism that involves protein-protein or protein-nucleic acid interactions. In fact, all of the HIV accessory proteins as well as the regulatory proteins Tat and Rev lack enzymatic activity. Thus, HIV accessory proteins behave like adaptor molecules that connect other viral or cellular proteins or nucleic acids to various preexisting cellular pathways, thereby changing their activity or specificity and thus controlling processes important for viral replication (for review see Strebel, 2003; Bour and Strebel, 2003).

Vpu is a small HIV-1-encoded membrane protein that enhances the release of progeny virions from infected cells and induces the degradation of the HIV receptor molecule CD4. These two functions of Vpu are mechanistically independent, yet both require protein-protein interactions. Indeed, the rapid degradation of the surface receptor CD4 in Vpu-expressing cells that reduces the half-life of CD4 from approximately 6 hr to less than 15 min is caused by the formation of a multiprotein complex consisting of Vpu, CD4, and β-TrCP. TrCP, in turn, is a component of the *S*kpI, *C*ullin, *F*-box protein (SCF^{TrCP}) E3 ubiquitin ligase complex whose normal function is to regulate the ubiquitination and proteasome degradation of cellular proteins such as β-catenin and IκB (Yaron et al., 1998; Spencer et al., 1999; Latres et al., 1999). However, in HIV-infected cells, Vpu—by virtue of its ability to simultaneously bind both TrCP and CD4—redirects the specificity of the SCF^{TrCP} complex to target CD4, which is normally degraded via a lysosomal pathway, into a proteasome-degradation pathway (Margottin et al., 1998).

Another function of Vpu is to increase progeny virus secretion from infected cells. Indeed, this is the activity of Vpu relevant to the current study by Hsu et al. (2004 [this issue of *Molecular Cell*]). In contrast to Vpu-induced degradation of CD4, which is fairly well understood in its mechanistic details, relatively little is known about how Vpu enhances virus release. Vpu—after cotranslational insertion into the host membrane—can self-assemble into homooligomeric complexes that in vitro function as ion-conductive membrane pores (reviewed in Bour and Strebel, 2003). The observation that mutations in Vpu that inhibited ion channel activity also affected the ability of the protein to enhance virus release suggested that these two activities of Vpu are functionally related. However, the question of how an ion channel

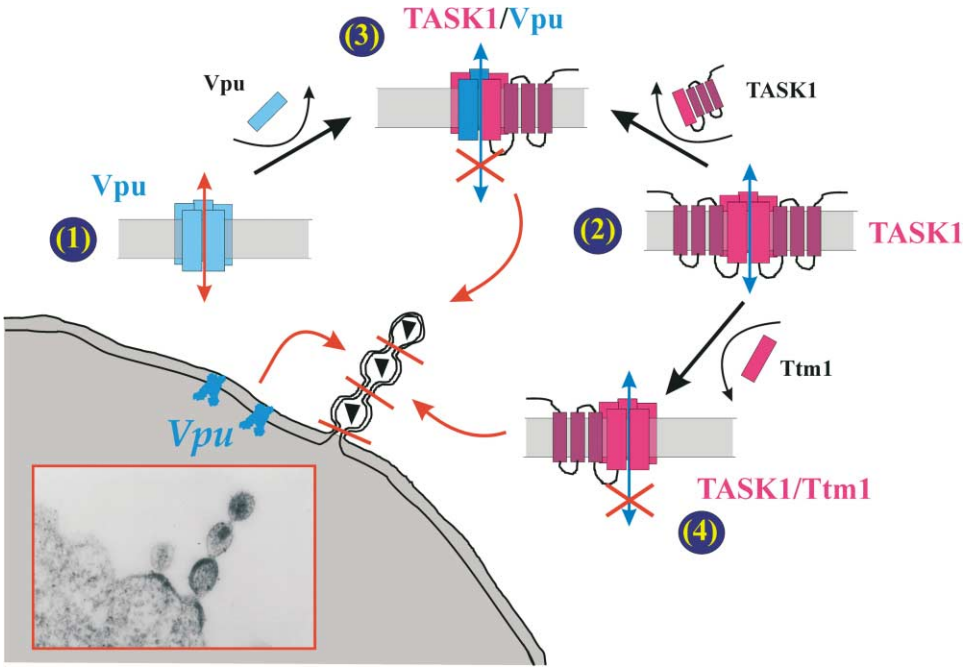

Figure 1. Mutual Inactivation of Vpu and TASK-1 Channel Activity

Both Vpu and TASK-1 have been ascribed ion channel activity. Previously, ion channel activity of Vpu was correlated with the efficient release of HIV virions (1). In the absence of Vpu, virus release is impaired and budding structures accumulate at the cell surface. In some instances, chain-like budding structures such as the one shown in the inset (EM image: Klimkait et al., 1990) were detectable, pointing to a defect in the viral detachment process. (2) TASK-1 is a cellular acid-sensitive K^+ channel. Hsu et al. (2004) report in their paper that coexpression of Vpu and TASK-1 results in the formation of heterooligomers (3). Such heterooligomers lack ion channel activity. Similarly, coexpression of TASK-1 with an N-terminal fragment, Ttm1, results in the formation of TASK/Ttm1 heterooligomers lacking ion channel activity (4). Both the inhibition of TASK-1 channel activity by Vpu (3) or Ttm1 (4) activates HIV virus secretion.

activity of Vpu could regulate virus release remained unresolved. More recent work by Varthakavi et al. (2003) shows that the requirement for Vpu for efficient virus release is host cell-dependent and points to an involvement of cellular factors in the Vpu-mediated virus release. In fact, Varthakavi et al. (2003) propose that Vpu functions to counteract a cellular factor that, in the absence of Vpu, inhibits virus release. Hsu et al. in their paper come to similar conclusions by identifying a host factor, TASK-1, whose expression inhibits HIV virus release. Interestingly, TASK-1 turns out to be an ion channel itself. In fact, it was the intriguing structural similarity of Vpu and the N-terminal transmembrane domain of TASK-1 that prompted Hsu et al. to investigate a possible functional interaction between these two proteins. Hsu et al. found in coimmunoprecipitation studies that the two proteins indeed physically interacted. Furthermore, expression of Vpu inhibited the ion channel activity of TASK-1 in a dose-dependent manner. This effect of Vpu was mimicked by a naturally occurring fragment of TASK-1, Ttm1; Ttm1 corresponds to the first transmembrane segment of TASK-1 and when coexpressed with TASK-1 inhibited its activity in a dose-dependent manner. Intriguingly, expression of Ttm1 in cells producing *vpu*-defective HIV rescued virus release with an efficiency that was comparable to or better than that of Vpu. The ability of Ttm1 to mimic Vpu function raises the intriguing possibility that Vpu enhances virus release not as previously thought by its own inherent channel activity but instead by interfering with the activity of another cellular ion channel (Figure 1). It will be interesting to see whether the species-specific function of Vpu reported by Varthakavi et al. can be correlated with the expression or activity of TASK-1. Also, the question remains, of course, how the TASK-1 ion channel activity interferes with HIV virus release. Electron microscopic data suggest that the inefficient release of virions in the absence of Vpu is caused by a defect in the detachment process (Klimkait et al., 1990). This could be due to altered membrane fluidity or the activity of other thus far unknown host factors. The identification of TASK-1 as a regulator of HIV virus release opens up an entirely new avenue that needs to be pursued and that some day may lead to a detailed understanding of the molecular mechanism governing HIV virus release.

Klaus Strebel
Viral Biochemistry Section
Laboratory of Molecular Microbiology
National Institute for Allergy and Infectious Diseases
National Institutes of Health
4 Center Drive, MSC 0460
Bethesda, Maryland 20892

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